Carrier screening for recessive conditions

This component of the Pan-Ethnic Carrier Screen tests 138 genes that cause autosomal recessive conditions. It is the most extensive carrier screen to date and includes conditions of mobility, developmental delay, visual impairment, hearing loss, intellectual disability, skin irregularities, joint and bone disorders, abnormalities of the nervous system, and numerous metabolic syndromes. None of these conditions has a cure, but some can be well managed with diet or medication (e.g. PKU or biotinidase deficiency). Many of these conditions, however, can result in a shortened lifespan or require continued medical care (e.g. Tay-Sachs disease or cystic fibrosis).

Carrier screening for X-linked conditions

This component of the test screens 10 genes that cause X-linked recessive conditions. This testing includes repeat analysis for fragile X syndrome, the most common genetic form of intellectual disability in males. Females who are carriers for one of these conditions are at risk to pass the disease on to their sons.

Approximately 5-8% of carrier individuals will have a normal SMN1 copy number of two, but both copies will be on the same chromosome (in cis) with deletion only; other pathogenic variants will not be detected.

Although a positive test result should not affect the health of the individual, she could be at a 25% risk for passing that condition on to her children depending on the carrier status of the partner. In addition to the specific pathogenic variants identified by the panel, Emory Genetics Laboratory also offers single-gene, full gene sequencing for genes on the panel, which can be utilized to screen partners of positive carriers. Knowing about these risks ahead of time can help couples make decisions about testing options prior to and during pregnancy, and can help healthcare providers be more readily prepared to offer appropriate follow-up care at delivery. While the specific risks will vary, the Pan-Ethnic Carrier Screen is appropriate for individuals of all ethnicities.

Methodology

Next Generation Sequencing: In-solution hybridization of all coding exons is performed on the patient’s genomic DNA. Although some deep intronic regions may also be analyzed, this assay is not meant to interrogate most promoter regions, deep intronic regions, or other regulatory elements, and does not detect single or multi-exon deletions or duplications. Direct sequencing of the captured regions is performed using next generation sequencing. The patient's gene sequences are then compared to a standard reference sequence. Only known pathogenic variants will be reported.
**RMRP** belongs to a family of genes called small miscellaneous non-coding RNAs. Full sequencing is not performed on this gene; rather only the single 70A>G mutation in this gene is analyzed.

**Fragile X Syndrome Repeat Analysis:** Both normal CGG repeat tracts and expanded CGG repeat tracts are detected by PCR amplification, using a CGG repeat-specific probe, and capillary electrophoresis. Expanded CGG repeat tracts will be reflexed to a gene specific PCR and sized by agarose gel electrophoresis.

**Spinal Muscular Atrophy (SMA) Testing:** *SMN1* gene deletions were quantified by multiplex ligation polymerase chain reaction amplification (MLPA) of exons 7 and 8. Gene dosage ratios of *SMN1* are calculated relative to the average of 16 reference loci and are expressed as gene dosage, and/or copy number. Diploid gene dose or 2 copies of *SMN1* indicates normal (not affected) status, 1x gene dosage or 1 copy of the *SMN1* gene most likely indicates carrier status and deletions (less than 0.1x) of *SMN1* or 0 copies of the *SMN1* gene designates affected status. This carrier assay tests for the common *SMN1* deletion only; other pathogenic variants will not be detected. *SMN2* copy number is not assessed.

**Deletion/Duplication Analysis:** DNA isolated from peripheral blood is hybridized to a gene-targeted CGH array to detect deletions and duplications. The targeted CGH array has overlapping probes that cover the entire genomic region. Please note that only the following genes are included in the deletion/duplication analysis component of this panel: *CFTR, DMD,* and *MECP2.*

**Alpha-thalassemia Analysis:** Copy number changes in the *HBA1* and *HBA2* genes are detected using multiplex ligation polymerase chain reaction amplification (MLPA). This assay identifies the hemoglobin Constant Spring (HbCS) mutation, as well as common deletions associated with alpha-thalassemia, including the 3.7, 4.2, Southeast Asian, Filipino, and Thailand deletions.

**Detection**

**Next Generation Sequencing:** Clinical Sensitivity: See results report. Pathogenic variants in regions other than the targeted area, including the promoter region, some mutations in the introns and other regulatory element mutations, cannot be detected by this analysis. Large deletions/duplications will not be detected by this analysis. Results of molecular analysis should be interpreted in the context of the patient's clinical/biochemical phenotype.

**For Fragile X Syndrome Repeat Analysis:** All cases of fragile X syndrome caused by CGG expansion will be detected by this assay. Rare cases of fragile X syndrome caused by other pathogenic variants in the *FMR1* gene will not be detected by this assay.

**For Spinal Muscular Atrophy (SMA) Testing:** Deletions of the *SMN1* gene are found in approximately 95% of individuals with SMA. This carrier assay tests for the common *SMN1* deletion only; other pathogenic variants will not be detected. Approximately 5-8% of carrier individuals will have a normal *SMN1* copy number of two, but both copies will be on the same chromosome (in cis) with a deletion on the second chromosome. This assay will not detect these carrier individuals. *SMN2* copy number is not assessed.

**Deletion/Duplication Analysis:** Detection is limited to duplications and deletions. The CGH array will not detect point or intronic mutations. Results of molecular analysis must be interpreted in the context of the patient's clinical and/or biochemical phenotype. Only the following genes are included in the deletion/duplication analysis: *CFTR, DMD,* and *MECP2.*

**Alpha-thalassemia Analysis:** This assay will detect the pathogenic variants specified above (Methodology Section), accounting for over 90% of alpha-thalassemia cases. The presence of less common deletions may also be detected by MLPA.

**Reference Range**

**For Fragile X Testing:**

Normal: Approximately 5-44 CGG repeats.
Intermediate: Approximately 45-54 unmethylated CGG repeats.
Premutation: Approximately 55-200 CGG repeats and methylation of expanded allele.
Affected: Over 200 CGG repeats and methylation of expanded allele.

**Specimen Requirements**

Submit only 1 of the following specimen types

**Type: Saliva**

Specimen Requirements:

Oragen™ Saliva Collection Kit.

Specimen Collection and Shipping: Store sample at room temperature. Ship sample within 5 days of collection at room temperature with overnight delivery.

**Type: Whole Blood**

Specimen Requirements:

In EDTA (purple top) tube:

Infants (Children (>2 years): 3-5 ml
Older Children & Adults: 5-10 ml.
Specimen Collection and Shipping: Ship sample at room temperature with overnight delivery.

**Type: Isolated DNA**

Specimen Requirements:

- In microtainer: 60 ug

Isolation using the Qiagen™ Puregene kit for DNA extraction is recommended.

Specimen Collection and Shipping: Refrigerate until time of shipment in 100 ng/ul of TE buffer. Ship sample at room temperature with overnight delivery.

**Related Tests**

- Pan-Ethnic Carrier Screen: Targeted Mutation Panel
- Ashkenazi Jewish Carrier Screen: Gene Sequencing Panel
- ACOG/ACMG Carrier Screen: Gene Sequencing Panel